MALARIA

Glenn Schnepf, MD, FACP
CAPT MC USN
Infectious Diseases

Objectives

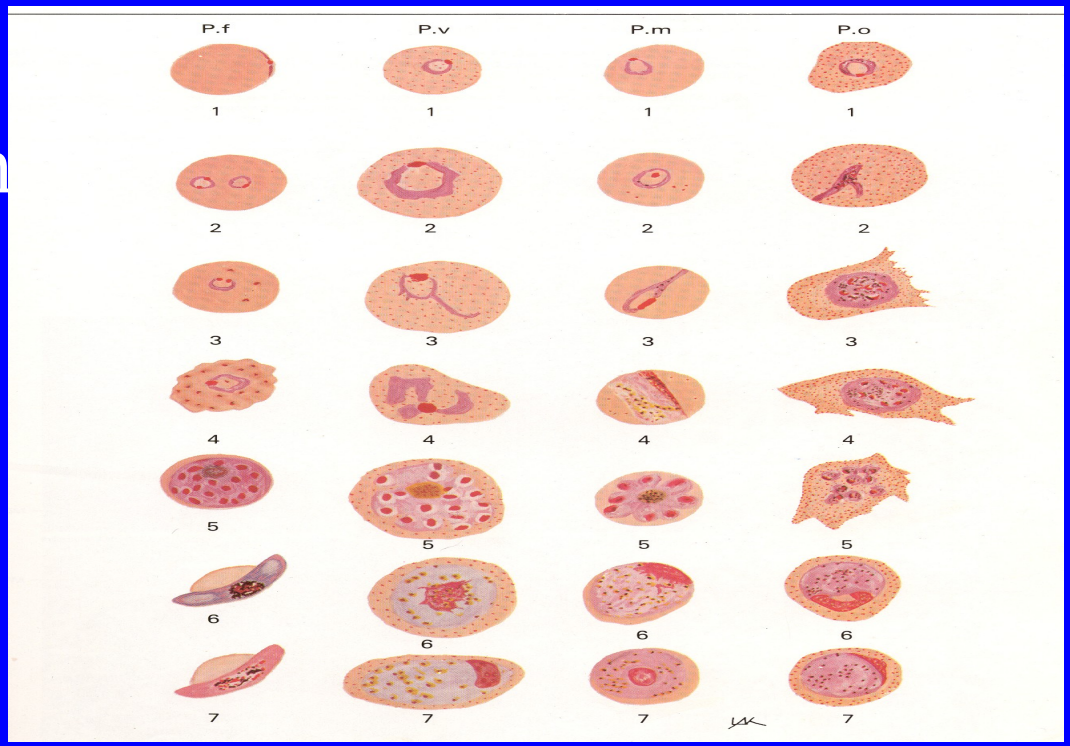
- Importance of malaria to the military
- Pathophysiology, host parasite relationships and life cycle of *Plasmodium* species
- Clinical manifestations of malaria
- Laboratory and diagnostic tests
- Treatment and prevention

Malaria

- Malaria – “bad air” from the marshes
- Splenomegaly with fever
  - Nei Ching Canon of Medicine (China 1700 BC)
  - Ebers Papyrus (Egypt 1570 BC)
- Endemic in US during 18th & 19th centuries
- 200 – 300 million cases worldwide per year
- 1 – 2 million deaths worldwide per year

MALARIA

- Genus: Plasmodium
- Species:
  - falciparum
  - vivax
  - ovale
  - malariae

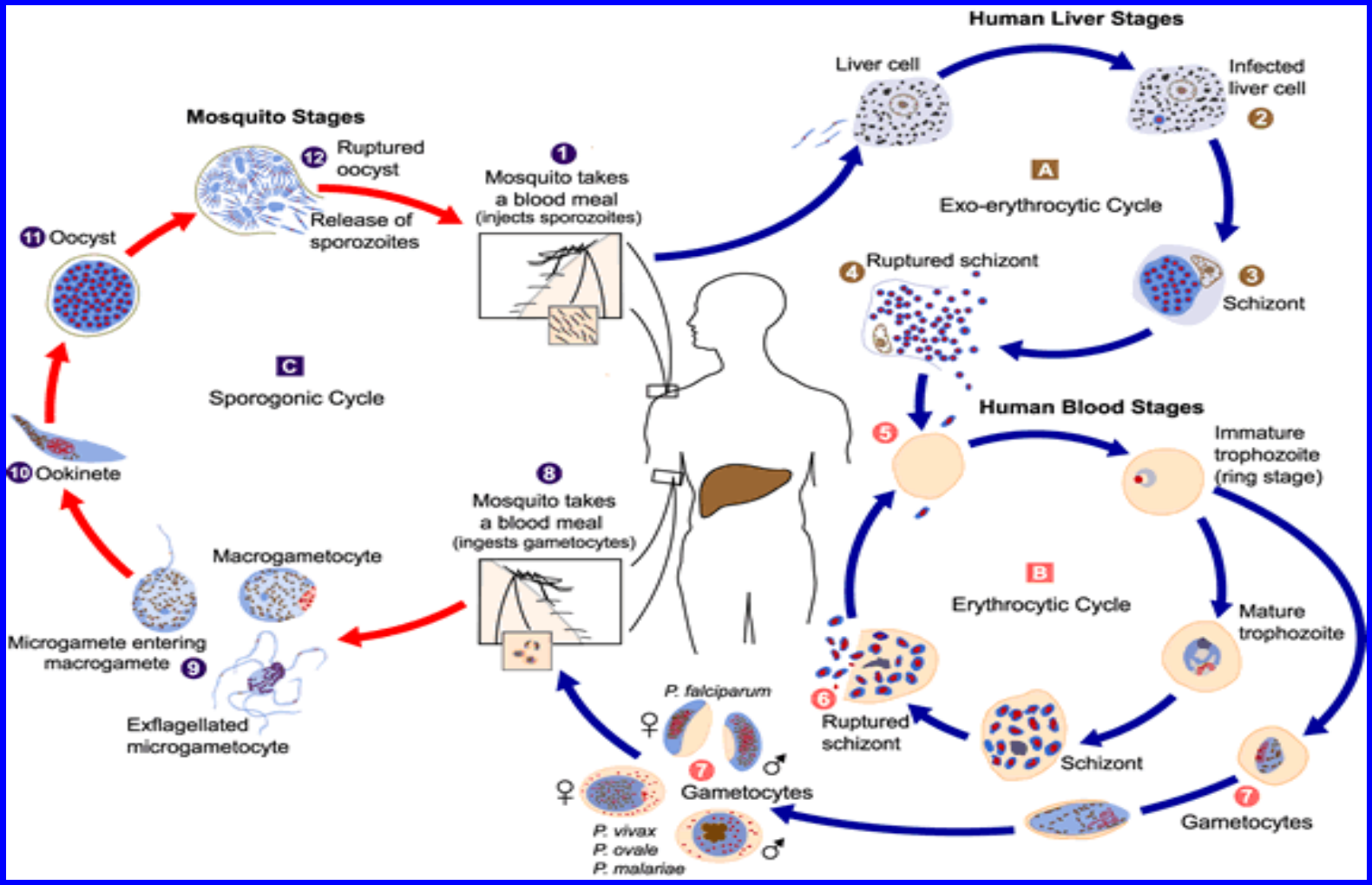


LIFE CYCLE

- Vector Phase: Anopheles mosquito

- Host Phase: Human and Simian
  - Exoerythrocytic (liver)
  - Erythrocytic (RBC)

Life Cycle


Human Liver Stages
Liver cell
Infected liver cell
2
A
Exo-erythrocytic Cycle
Ruptured schizont
4
3
Schizont
Human Blood Stages
5
Immature trophozoite (ring stage)
B
Erythrocytic Cycle
Mature trophozoite
6
Ruptured schizont
Schizont
7
Gametocytes
Gametocytes
P. falciparum
P. vivax
P. ovale
P. malariae
8
Mosquito takes a blood meal (ingests gametocytes)
Macrogametocyte
Microgamete entering macrogamete
9
Exflagellated microgametocyte
10 Ookinete
11 Oocyst
12 Ruptured oocyst
Release of sporozoites
Mosquito Stages
1
Mosquito takes a blood meal (injects sporozoites)
C
Sporogonic Cycle

INCUBATION

- P. falciparum: 10 days - 3 months
- P. vivax: 2 weeks - 12 months
- P. ovale: 2 weeks - 12 months
- P. malariae: 5 weeks - 3 years
- Seasonal variability with temperate climates

CLINICAL ASPECTS

- Release of merozoites from red cell lysis
- Malarial cycle:
  - cold or chilling stage
  - hot stage
  - sweating stage
  - resting stage

Fever Periodicity

- Synchronized release of merozoites
- *P. vivax* - tertian
- *P. malariae* - quartan
- *P. falciparum* - tertian
- Takes 1-2 weeks for non-immune patients
- Rare non-endemic areas

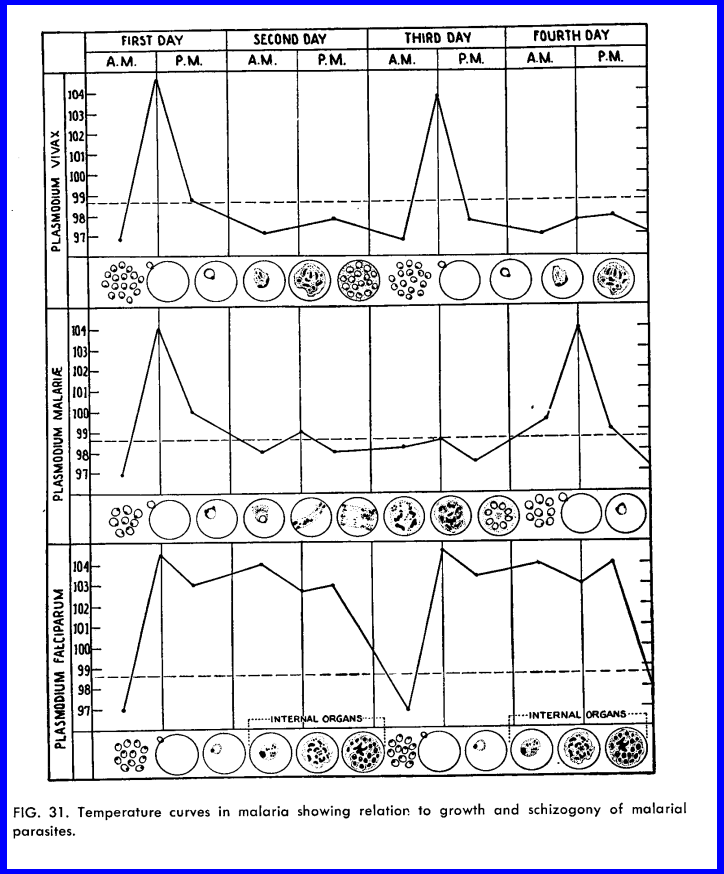


FIG. 31. Temperature curves in malaria showing relation to growth and schizogony of malarial parasites.

Recurrent and Persistent Infections

- Relapse
  - Dormant (hypnozoite) stages in liver
  - Only *P. vivax* and *P. ovale*
- Recrudescence
  - Incomplete treatment or partially effective host immune responses
  - Occurs with any of the four species, but most frequently with *P. falciparum*

Recurrent and Persistent Infections

- Reinfection
  - Areas of intense transmission
  - Most frequently with *P. falciparum*
- Multiple infections
  - Areas of intense transmission
  - Sub-Saharan Africa
- Persistent infection
  - *P. malariae*
  - Infection below detectable levels for 20 - 30 years

TARGETED RBCs

- Young RBCs - P. vivax and P. ovale
- Old RBCs - P. malariae
- Old and young - P. falciparum

LABORATORY FINDINGS

- Positive thick and thin smear
- Reflection of degree of hemolysis
  - ↓ Hemoglobin, hematocrit, haptoglobin
  - ↑ lactic dehydrogenase, reticulocytes
  - – Thrombocytopenia
  - – P. falciparum:
    - proteinuria, hemoglobinuria, ↑ serum creatinine, hypoglycemia

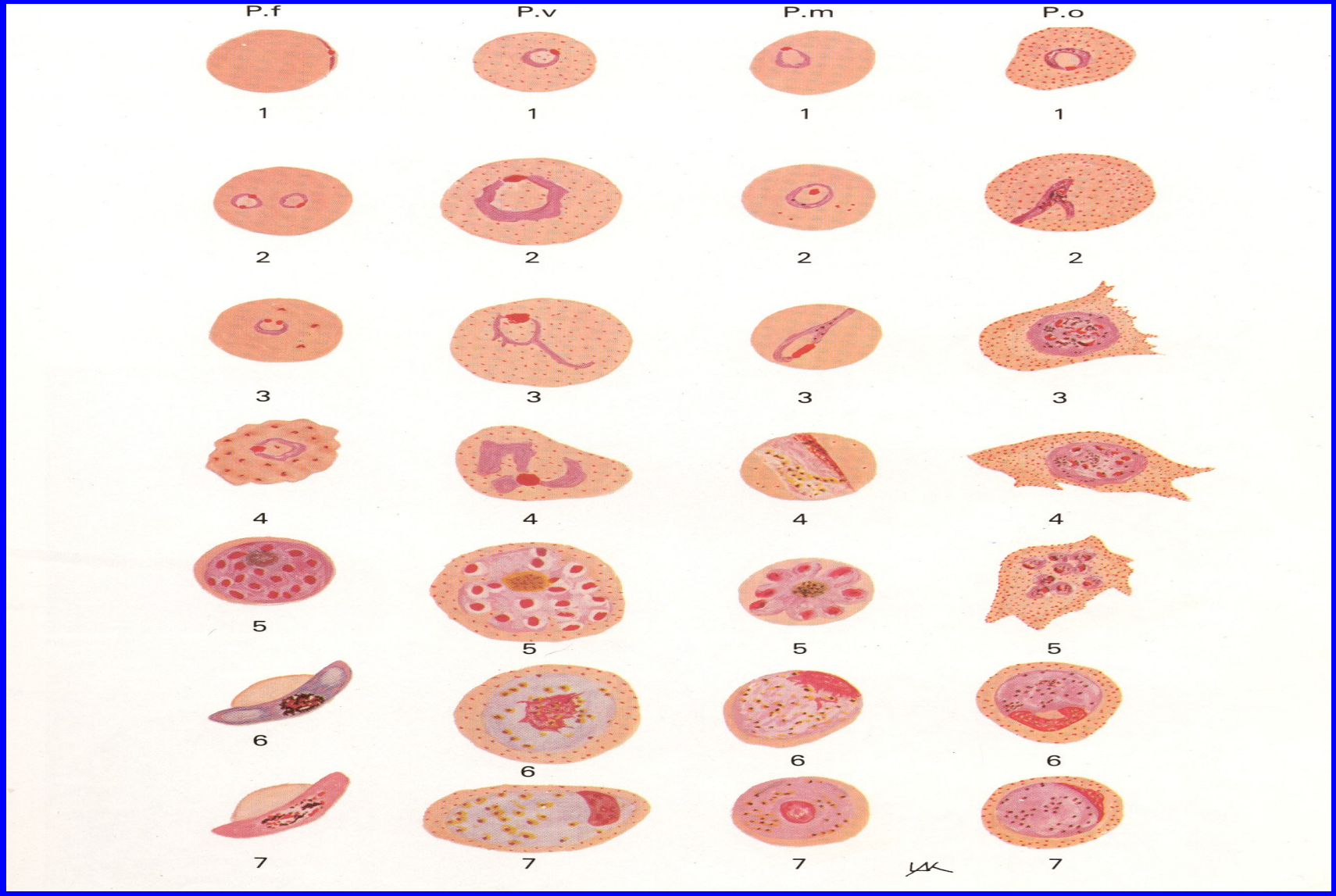
DIAGNOSIS

- Thick and thin smears - Gold Standard
  - Most reliable and least expensive ($0.02)
- Quantitative Buffy Coat ($0.83)
- Acridine orange stain ($0.06)
- Parasight®-F test - ($2.25)
- Serology
  - Not for acute cases

BLOOD SMEARS

- Thick and thin smears
  - 98% sensitive
  - 100% specific
  - species specific
- QBC
  - 95% sensitive
  - 100% specific
  - more rapid, not species specific

Plasmodium Species



Differential Diagnosis – Peripheral Smear

	P. falciparum	*P. vivax & P. ovale*
Multiply-infected RBCs	Common	Rare
Mature parasites (trophozoites and schizonts)	Absent	Common
RBC enlargement	Absent	Common

Plasmodium vivax

- Predominant: Latin America, Indian Sub-continent
- Common: South America, Oceania Southeast Asia
- Rare: Africa (lack of Duffy Coat antigen)

RBC Enlargement

- Present in *P. vivax*
- Absent in *P. falciparum*
- Schufner's dots
- 24 merozoites per schizont

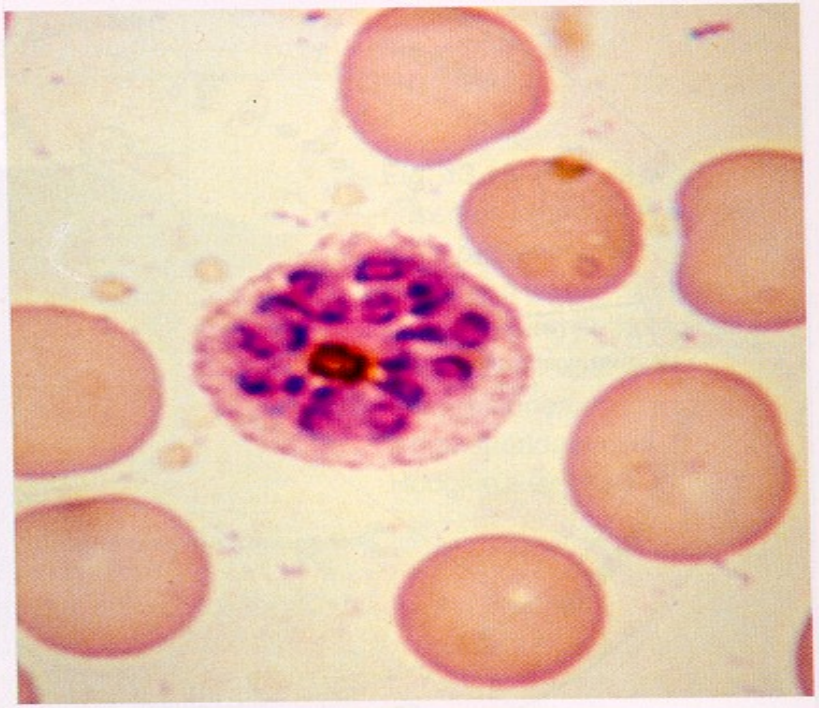
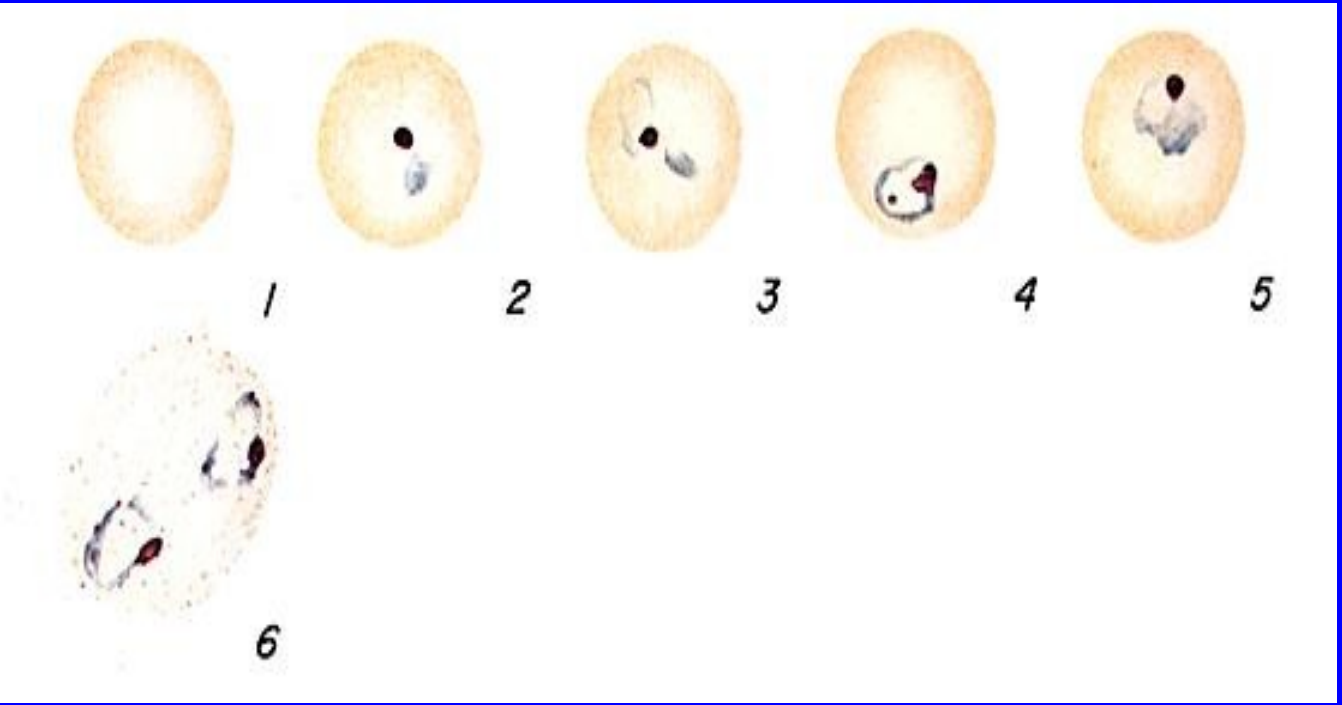
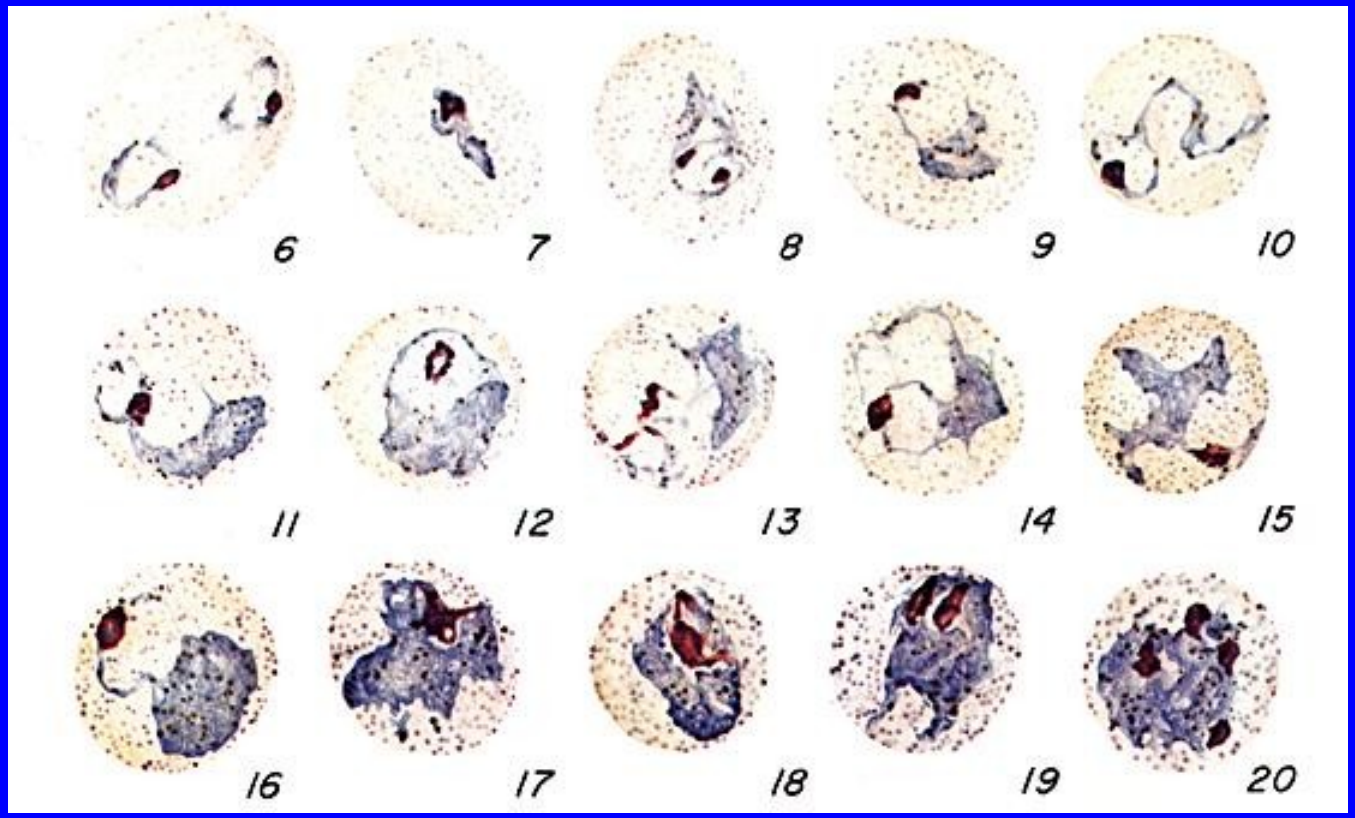


Fig. 13.26 Malaria. Thin blood film showing fully developed schizont of *P. vivax* with merozoites ready to burst out. Giemsa stain. See fig 13.21 for source.

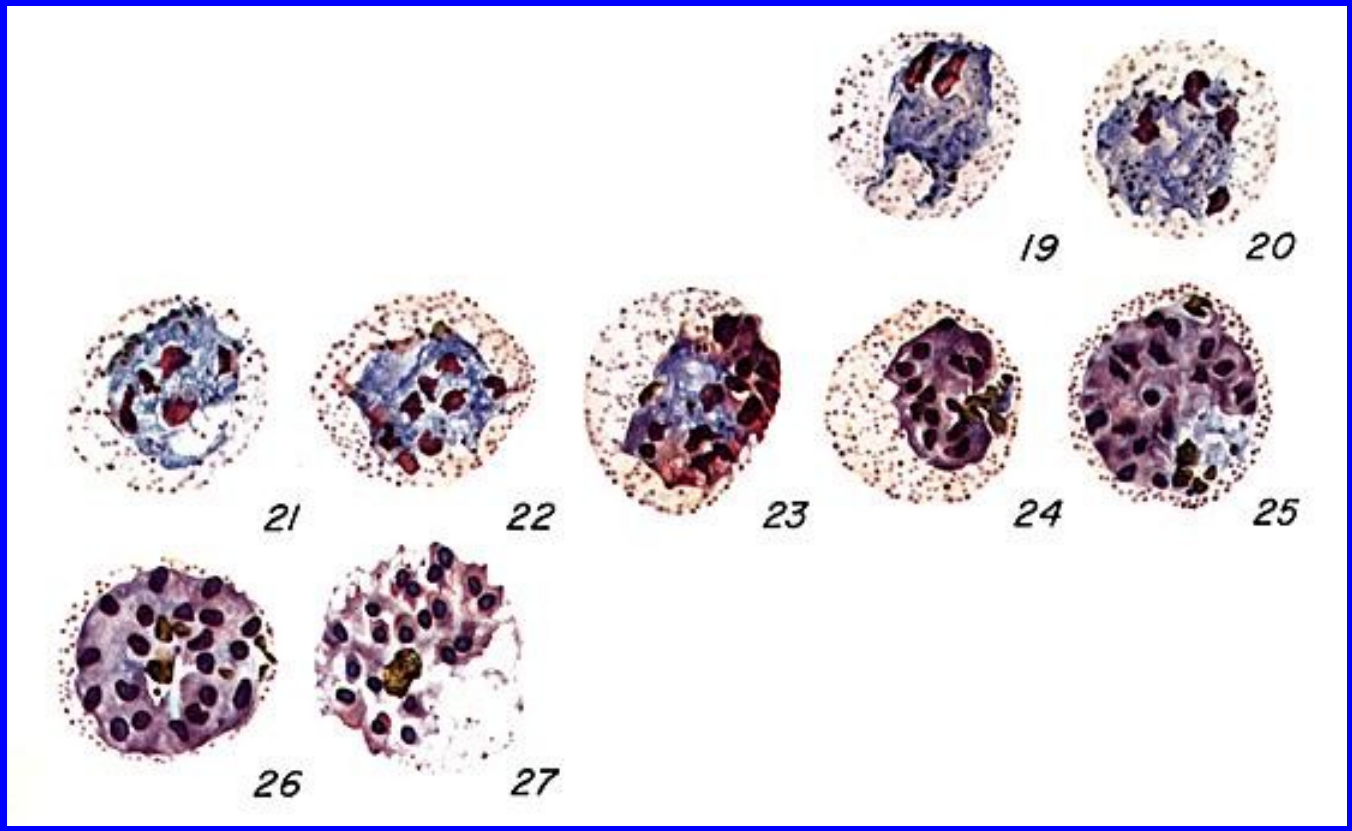
P. vivax ring



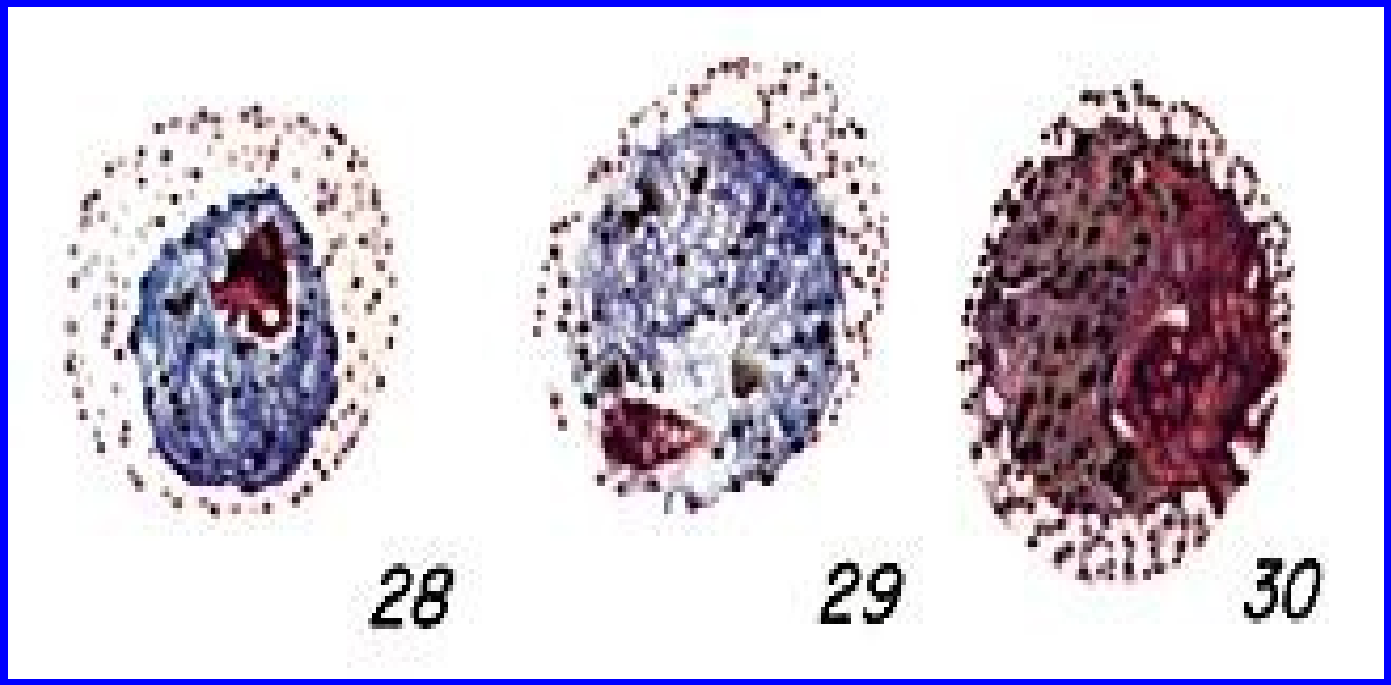
P. vivax trophozoites



P. vivax schizonts



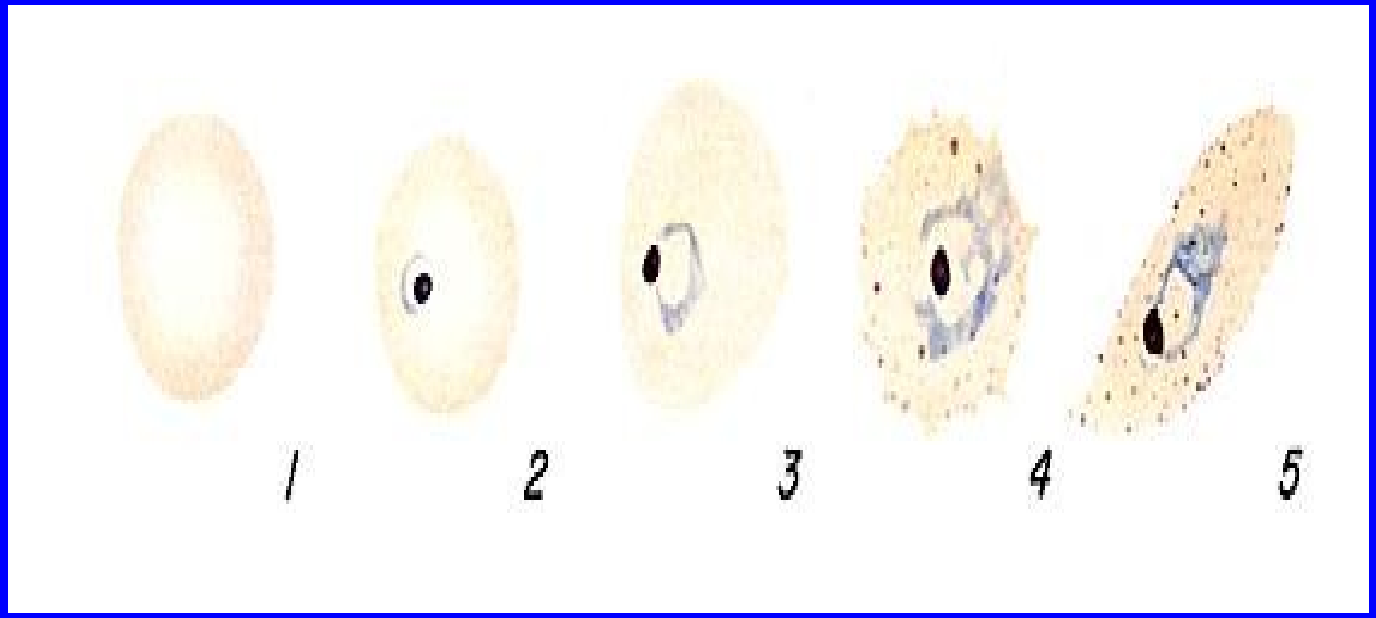
P. vivax gametocytes



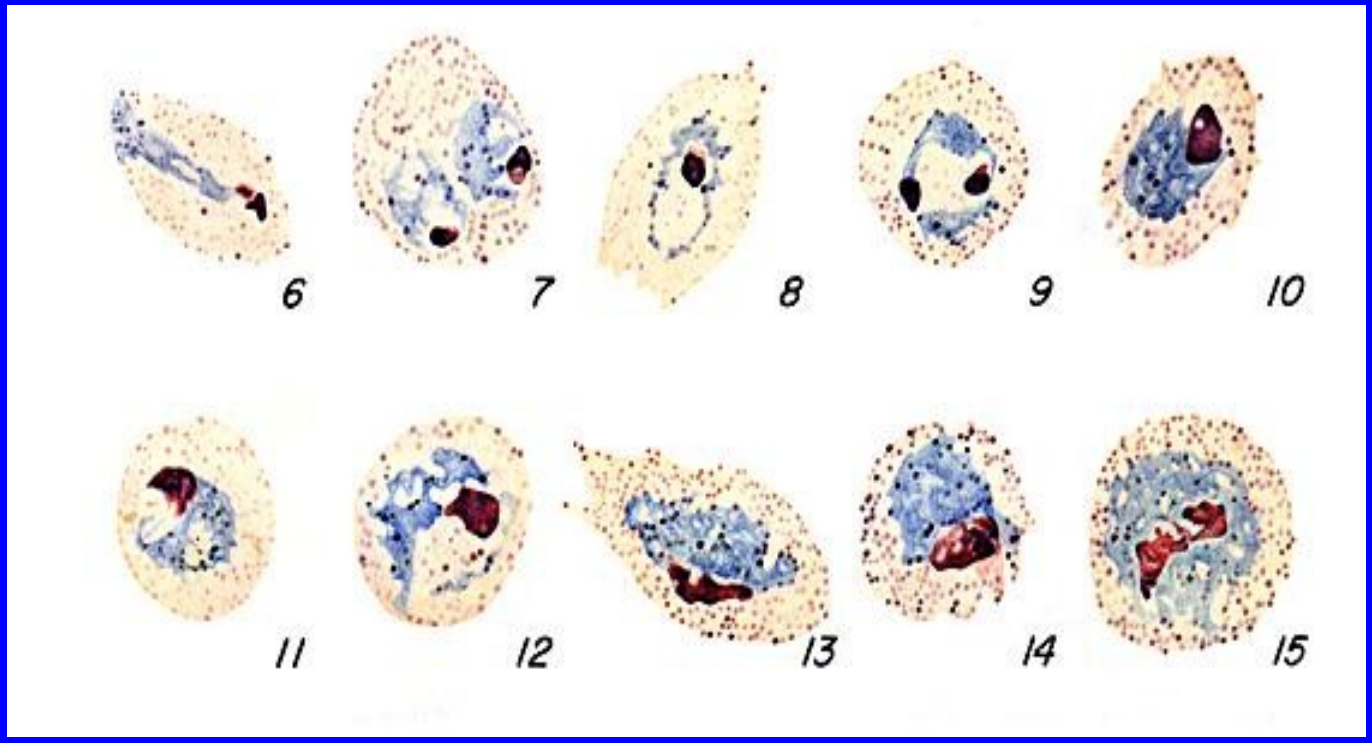
Plasmodium ovale

- Africa
- Early trophozoite – ring form
- Enlarged red blood cell and Schufner’s dots
- Developing schizont with jagged edges: fimbriated
- Mature schizont with six merozoites

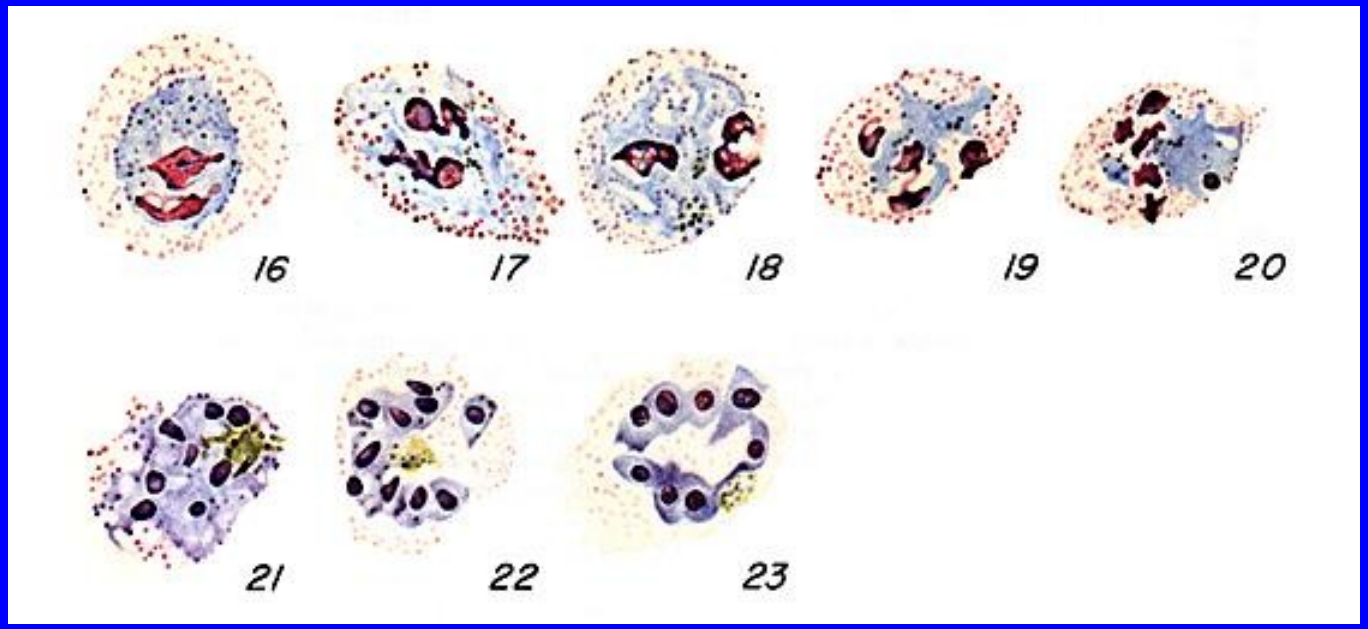
P. ovale ring



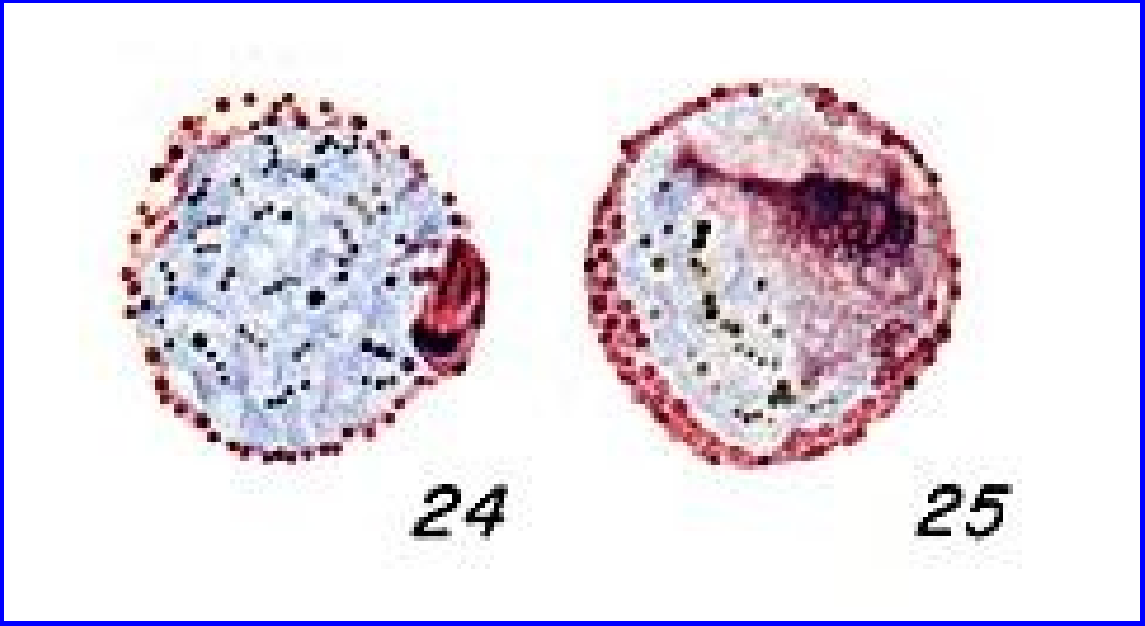
P. ovale trophozoite



P. ovale schizonts



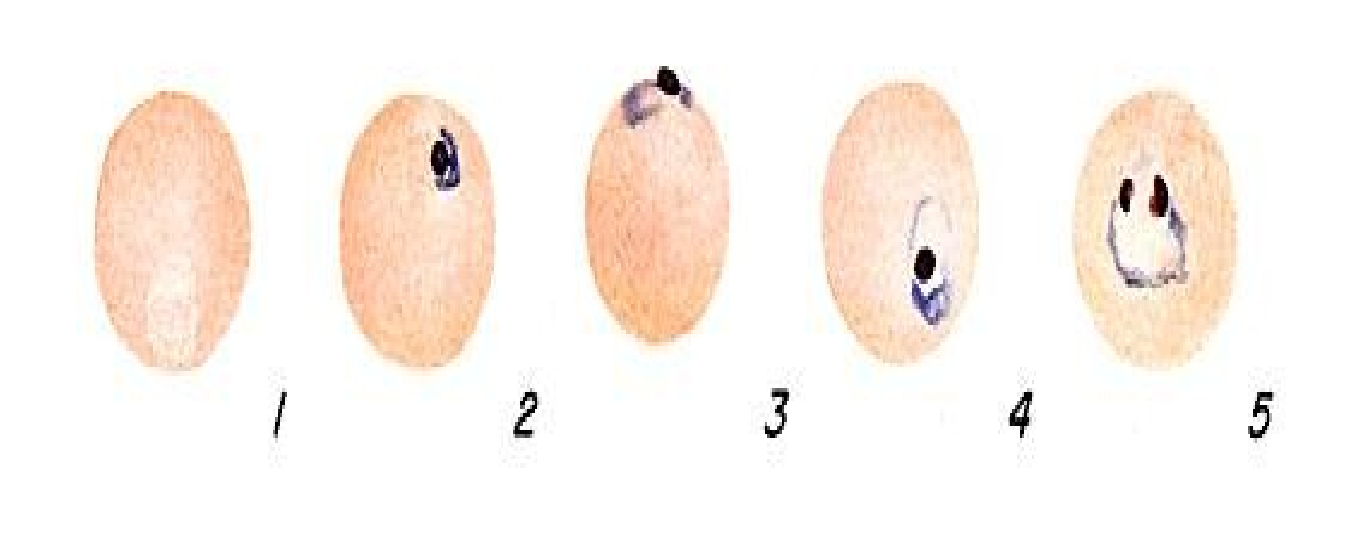
P. ovale gametocytes



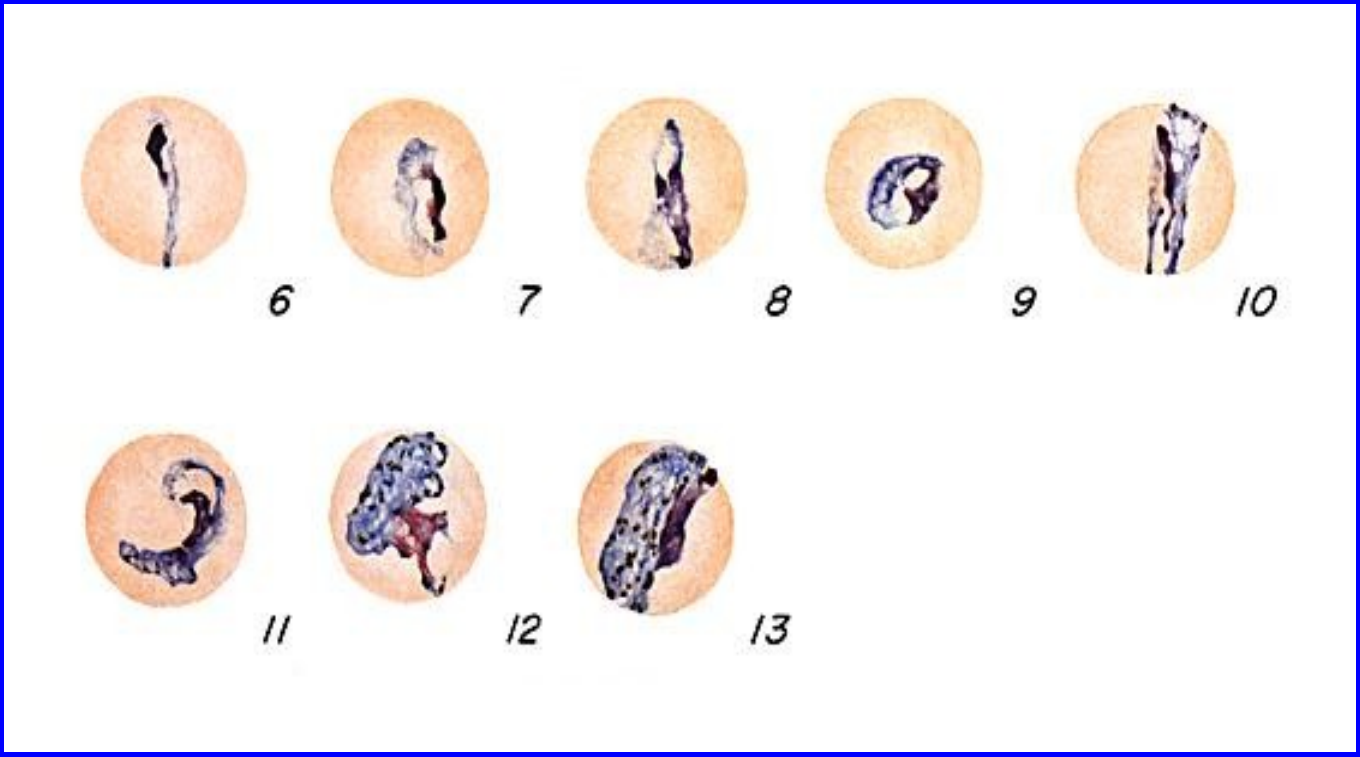
Plasmodium malariae

- Widespread
- Attacks older RBCs
- Late trophozoite with band form

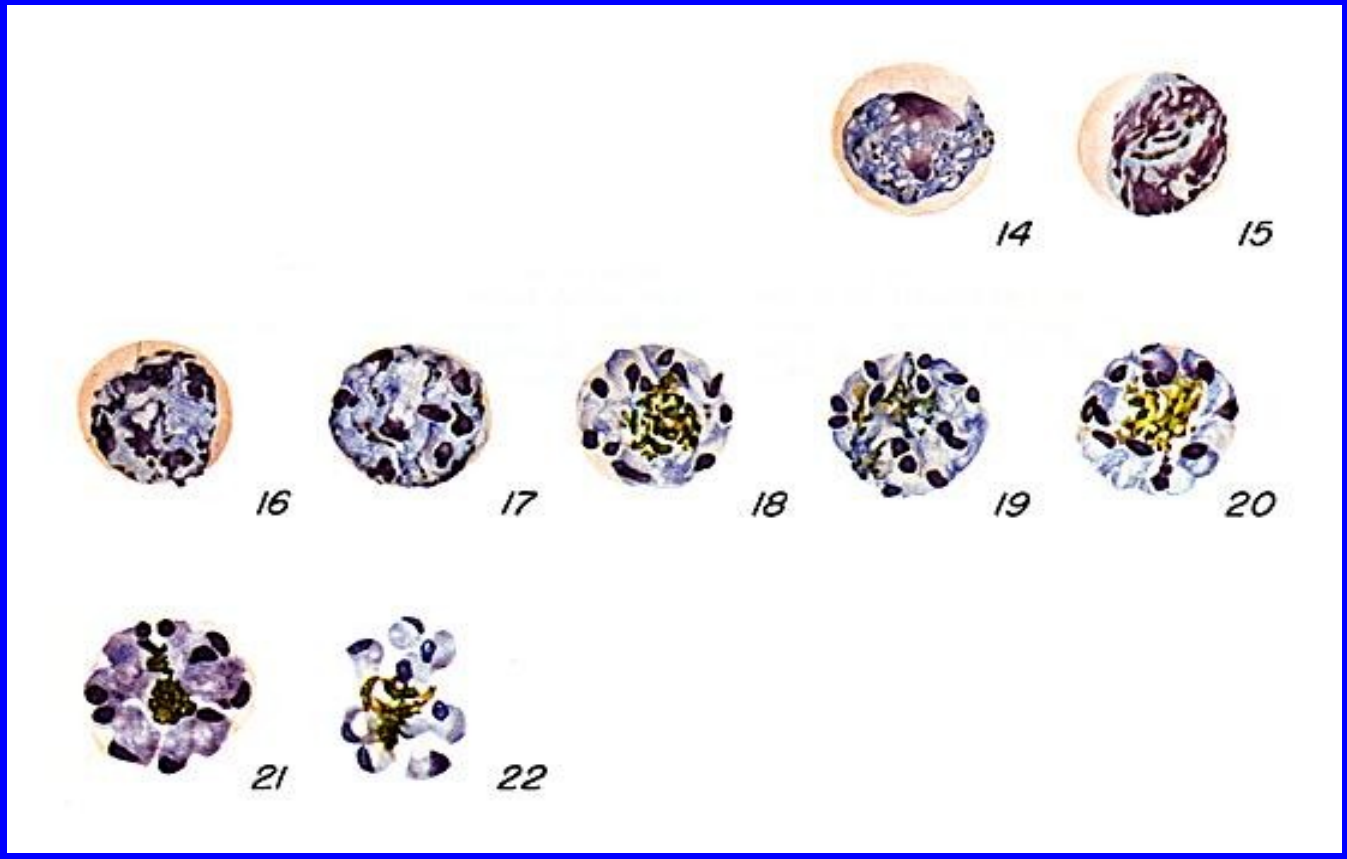
P. malariae ring stage



P. malariae trophozoite



P. malariae schizonts



P. malariae gametocytes

Plasmodium falciparum

- Predominant: Africa, Haiti
  Papua New Guinea

- Common: South America, Oceania,
  Southeast Asia

Mature Parasites in *P. falciparum*

- Present in heavy parasitemia
- Multiple ring forms in RBC
- Appliqué forms
- Delicate ring forms
- Banana-shaped gametocytes

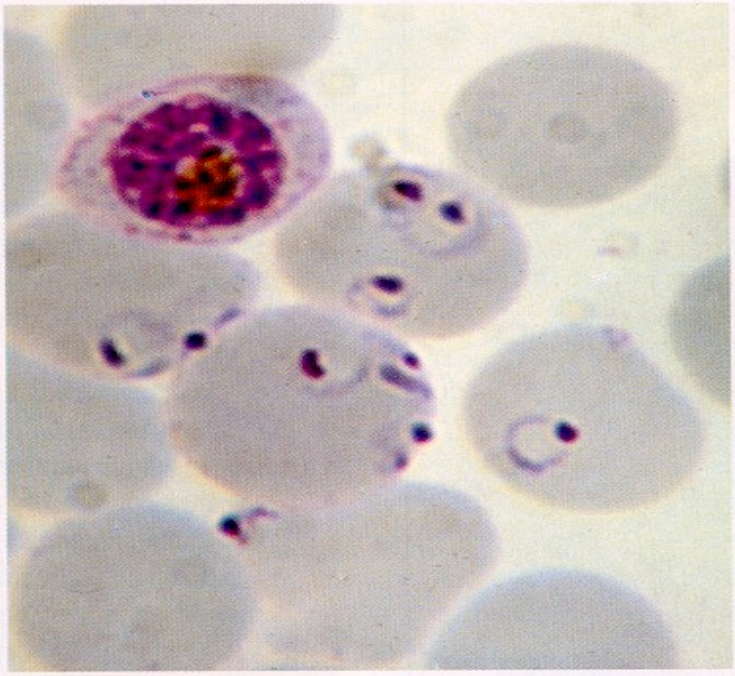


Fig. 13.25 Malaria. Thin blood film showing several ring forms and a schizont of *P. falciparum*. This is only seen in severe cases. Giemsa stain. See fig 13.21 for source.

RBC Enlargement

- Absent in *P. falciparum*
- Lack of schizonts
- Attacks RBCs of all ages
- Sequesters in the capillaries
- Brain & kidney damage

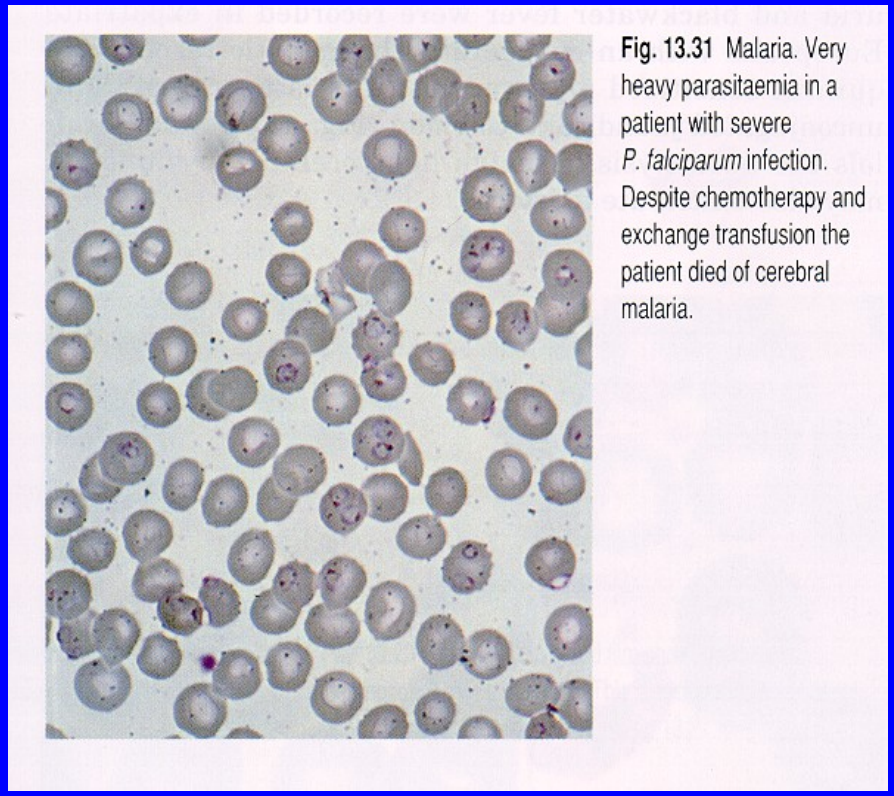
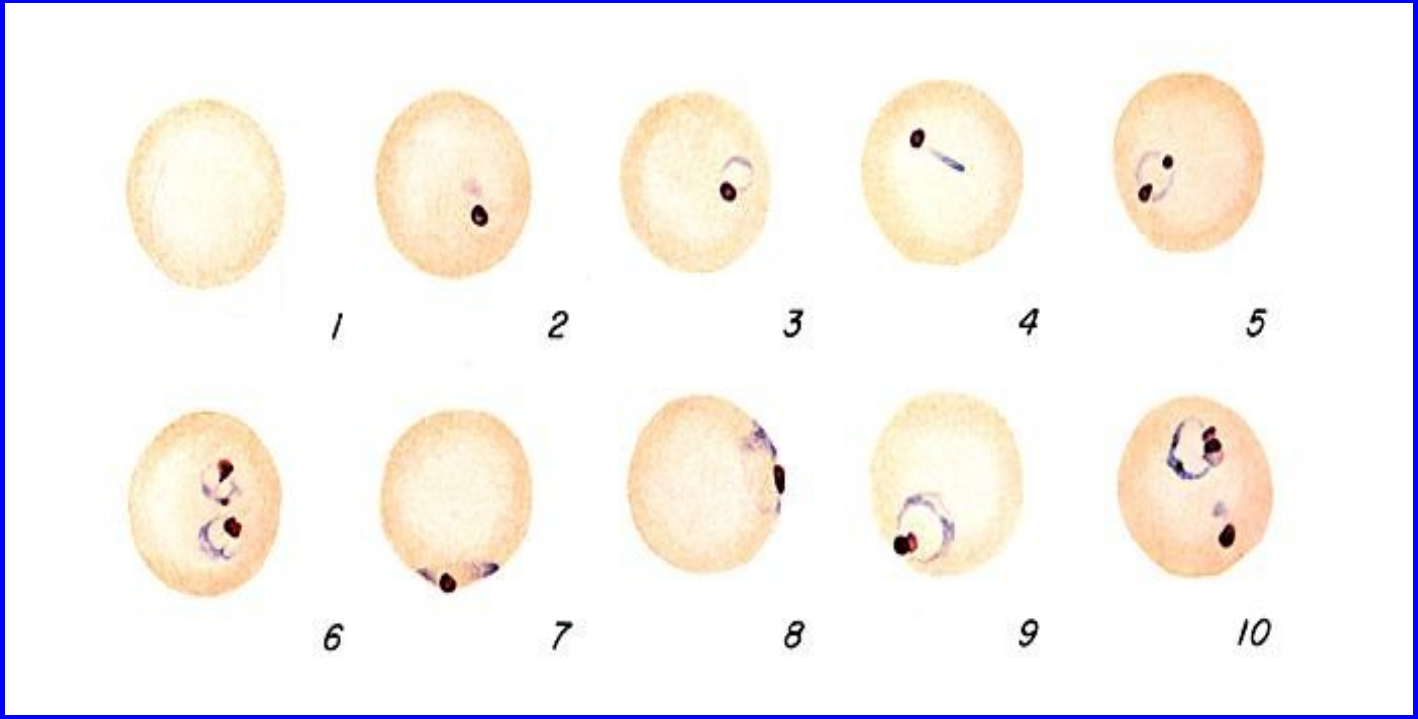
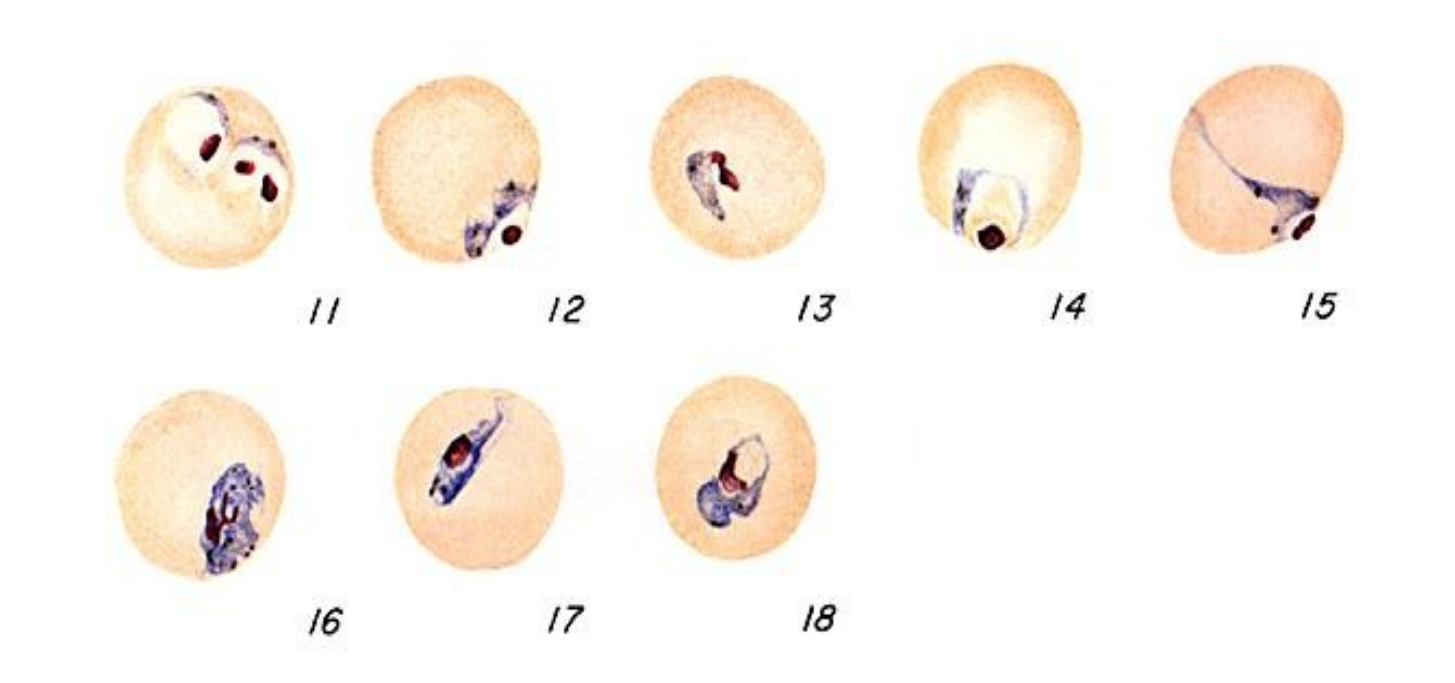


Fig. 13.31 Malaria. Very heavy parasitaemia in a patient with severe *P. falciparum* infection. Despite chemotherapy and exchange transfusion the patient died of cerebral malaria.

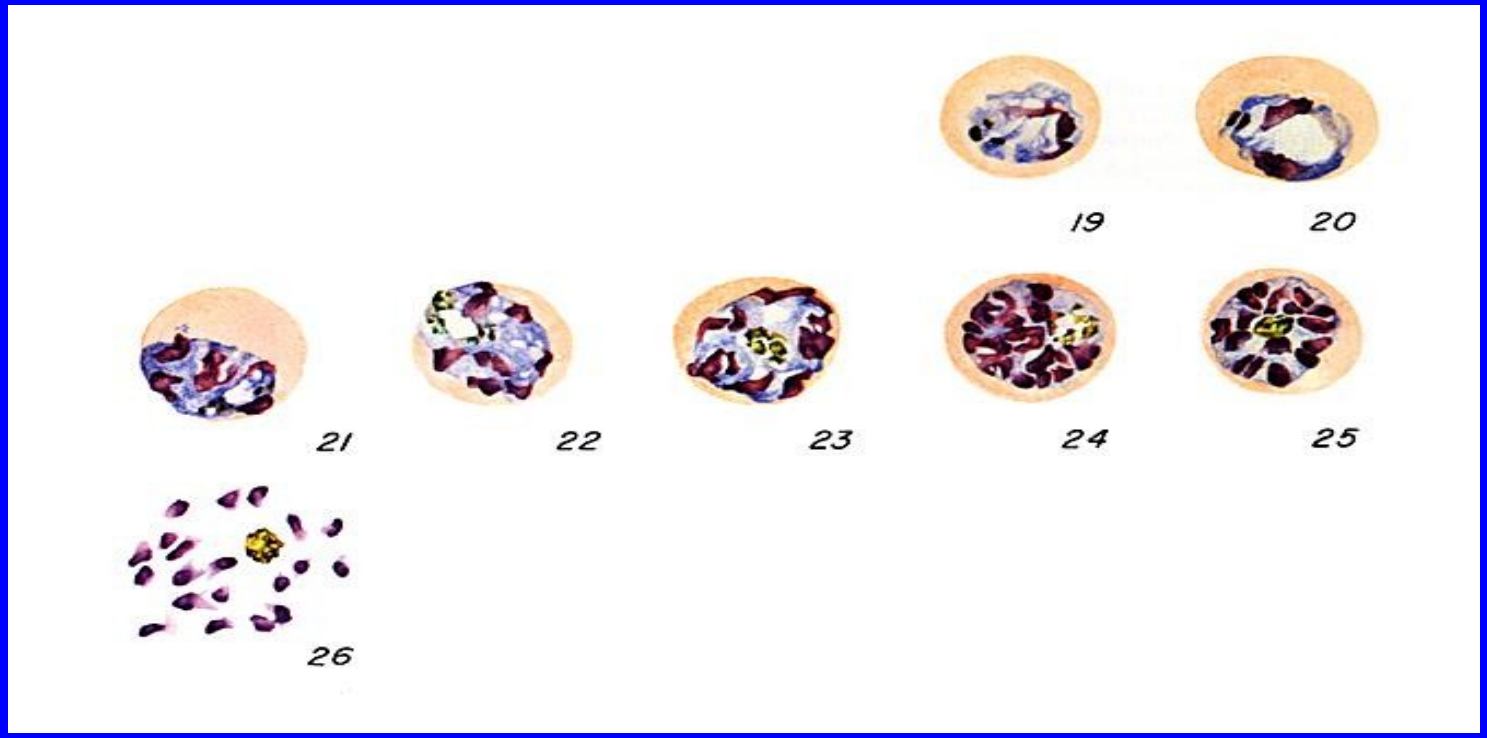
P. falciparum ring



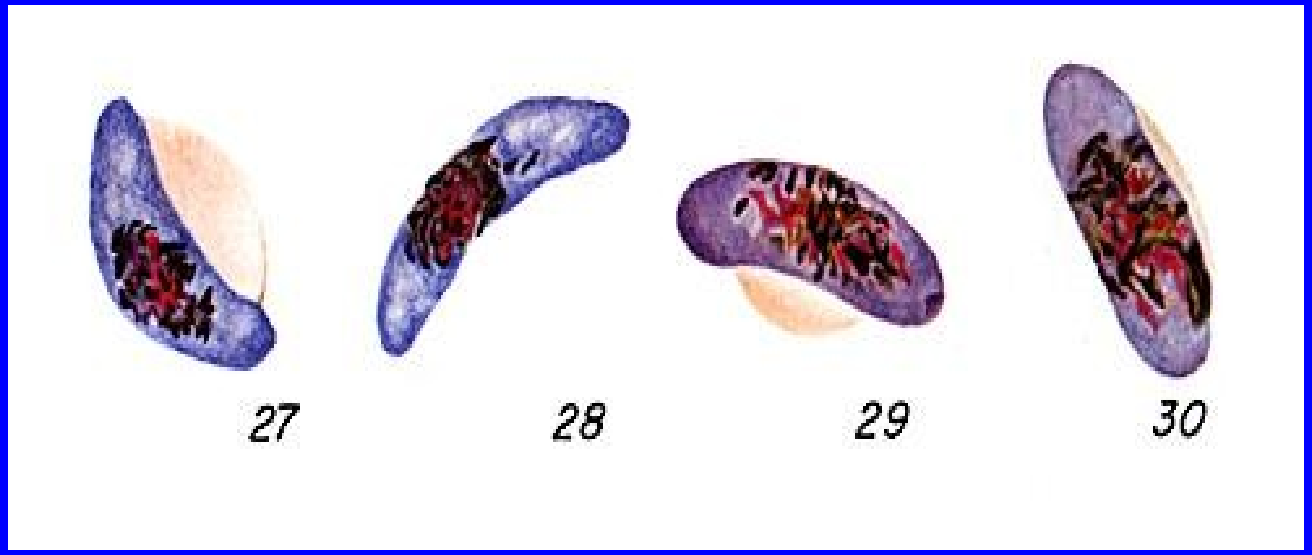
P. falciparum trophozoites



P. falciparium schizonts

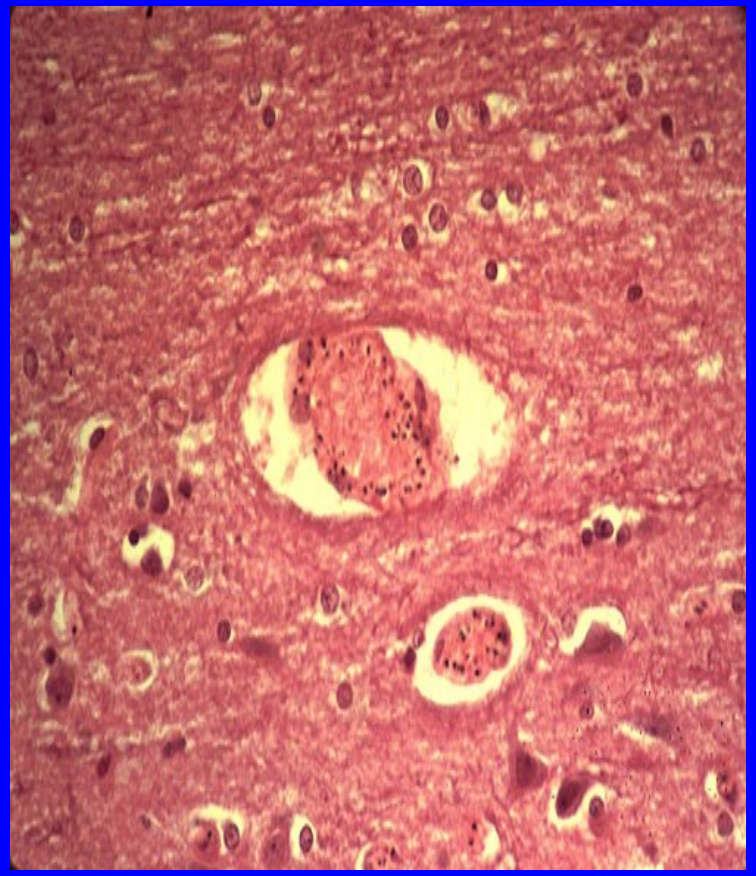


P. falciparium gametocytes



Cerebral Malaria

- Organism lining the inside wall of blood vessels
- Capillary congestion
- Perivascular hemorrhages
- Organisms stain brown-black



PERSONAL PROTECTIVE MEASURES

- To avoid mosquitoes - don’t go
- Insect repellants
  - DEET - 20 - 35% lotion
  - Permethrin - spray on bed nets
- Mosquito nets
- Window screens/air conditioned rooms

Malaria in US Troops in Somalia

- 112 cases - Jan-Dec 1993
  - P. vivax (87%)
  - P. falciparum (7%)
- Risk factors
  - noncompliance with chemoprophylaxis - 56%
  - failure to use bed nets
  - failure to keep sleeves rolled down
  - guard duty along river > 7 nights

Malaria in US Troops in Liberia

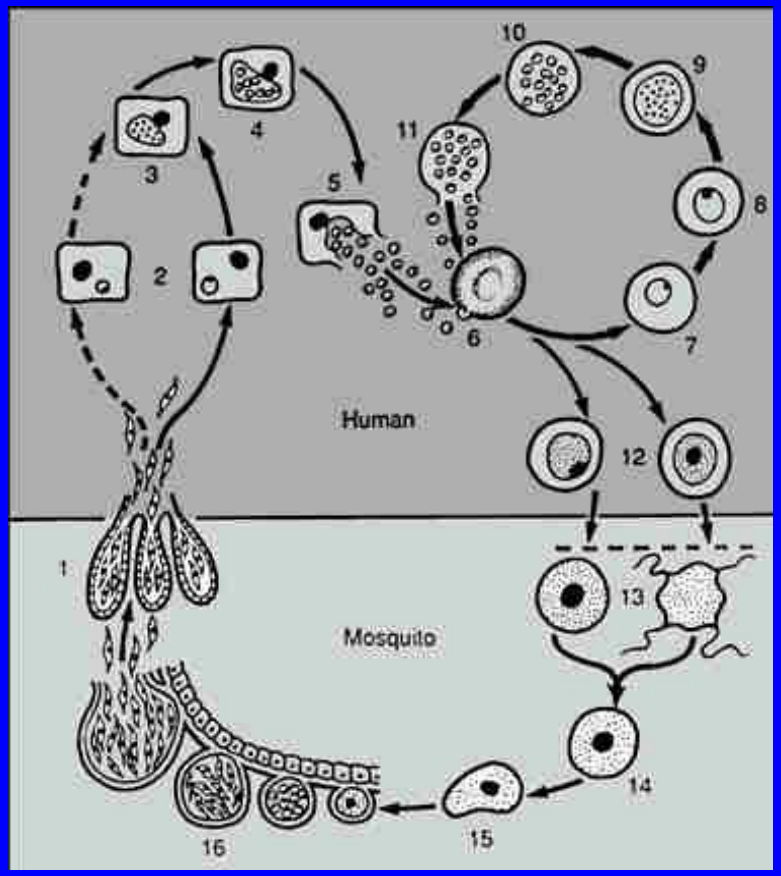
- 290 total JTF Personnel ashore in Liberia
- 80 malaria cases treated
  - 71 Marines, 7 Navy, 1 Army and 1 civilian
  - 51 cases confirmed by positive smear
  - 29 cases presumed by clinical criteria
  - Historical predicted risk is 11-50% for unprotected personnel
  - Personal Protective Measures
    - 7/133 (5%) (tested had protective levels of Mefloquine)
    - 19/290 (7%) surveyed had used DoD issued DEET formulation
    - 36/290 (12%) surveyed had permethrin treated uniforms
    - Bed nets were not carried ashore

VACCINE DEVELOPMENT

- Sporozoite antigens (CSP)
- Merozoite surface proteins (MSP)
- Erythrocyte binding antigen (EBA)
- Gametocyte antigens
- DNA based vaccines
- An effective vaccine will need at least three antigens

Plasmodium Life Cycle

- Trophozoites
  - 7,8. Ring
  - 9
- 10. Schizonts
  - Lyse RBCs
  - **11.Release merozoites**
- 12. Gametocytes
- 13-16. Cycle in vector



CHEMOPROPHYLAXIS

- 90% efficacious
- Compliance is poor
- Need to continue four weeks after returning
- Chloroquine - start two weeks before trip
- Mefloquine - start two weeks before trip
- Doxycycline - start two days before trip
- Primaquine - start after return - hypnozoites

CHEMOPROPHYLAXIS

- CHLOROQUINE - *ARALEN*
  - Once weekly in areas with sensitive organisms
  - 500 mg (salt)/300 mg (base)
  - GI upset, headache, blurred vision, myopathy
  - No serious eye damage reported
  - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- MEFLOQUINE - *Lariam*
  - Once weekly in Plasmodium sensitive areas
  - 250 mg weekly
  - GI upset, Insomnia, vivid or bad dreams
  - Neuropsych and spatial orientation problems
  - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- DOXYCYCLINE - *Vibramycin*
  - Daily in chloroquine/mefloquine resistant areas
  - 100 mg daily
  - GI upset, monilial vaginitis, photosensitivity
  - Not for use in children and pregnancy
  - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- PROGUANIL - *Paludrine*
  - Alternative to chloroquine/mefloquine resistant areas in Africa (not FDA-approved)
  - 200 mg daily combined with chloroquine
  - Anorexia, vomiting, diarrhea, mouth ulcers
  - Safe for use in children and pregnancy
  - Follow-up with 2 weeks of Primaquine after leaving areas of high density parasites & risk

CHEMOPROPHYLAXIS

- PROGUANIL + ATOVAQUONE – *Malarone*
  - Prophylaxis for *P. falciparum*
  - Little data on *P. vivax*
  - 1 tab (100 mg + 250 mg) po qd with food
  - Take 2 days before travel, every day in malarious area and one week after return
  - Adverse effects: Abd. Pain – 17%, N/V – 12%, headache – 10%, asymptomatic ↑ ALT/AST

CHEMOPROPHYLAXIS

- PRIMAQUINE - *Primaquine*
  - Eradicates P. vivax or P. ovale from liver stage
  - 26.3 mg (salt)/15 mg (base)
  - Hemolysis in G6PD deficiency, GI upset
  - Not safe for use in pregnancy
  - Give for 2 weeks after leaving areas of high density parasites & risk - not for everyone

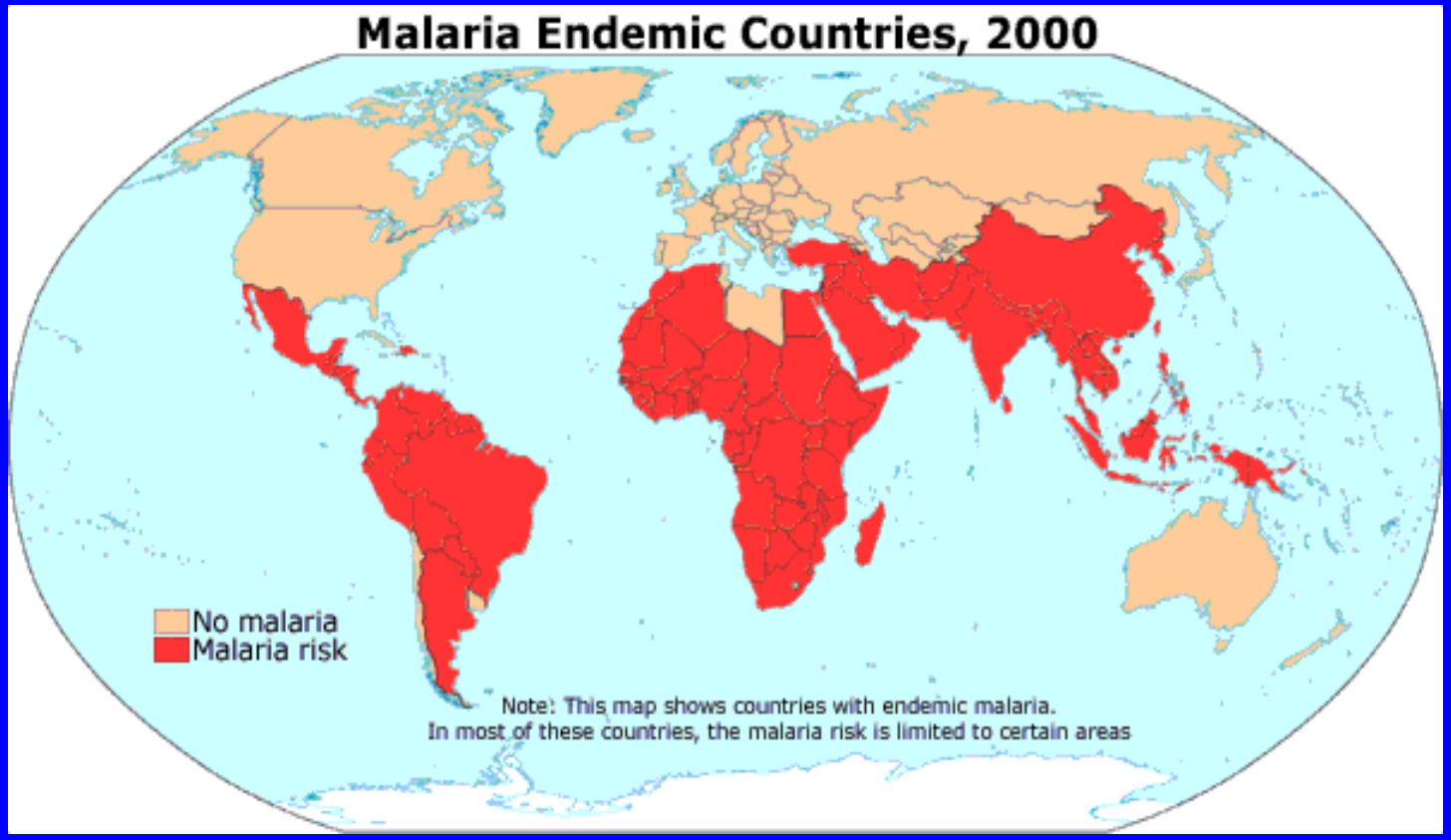
Classes of Anti-Malarial Medications

- **Blood Schizontocide**
  - **Chloroquine, Quinine, Quinidine, Mefloquine, Halofantrine, Sulfonamides, Tetracyclines, Atovaquone, Artemisinin compounds**
- **Tissue Schizontocide**
  - **Primaquine, Proguanil, Pyrimethamine**
- **Gametocide**
  - **Primaquine**
- **Hypnozoitocide**
  - **Primaquine**

TREATMENT

- Chloroquine
- Quinidine + doxycycline
- Mefloquine
- Fansidar - indigenous pop. or emergency
  - Three tabs po at one time
- Complete with 14 days of primaquine
  - May have had undetected dual infection

Geographic Distribution


Malaria Endemic Countries, 2000
No malaria
Malaria risk
Note: This map shows countries with endemic malaria.
In most of these countries, the malaria risk is limited to certain areas

CHLOROQUINE SENSITIVE

- Most non-falciparum species
- Caribbean
- Central America - not east of canal zone
- Middle East and Egypt

- Resistance seen in Papua New Guinea

CHLOROQUINE RESISTANT

- Most falciparum species
- Africa
- Southeast Asia - mefloquine resistance
- Central America - east of canal zone
- South America

Malaria

- Questions ?